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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/962,094	10/31/1997	PATRICIA A. BILLING-MEDEL	5995.US.P1	8450

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/962,094	BILLING-MEDEL ET AL.	
	Examiner	Art Unit	
	Jehanne S Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-82,85 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-82, 85, 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 30, 2004 has been entered.

2. Currently, claims 80-82 and newly added claims 85-86 are pending and under consideration in the instant application. Claims 83 and 84 are cancelled. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is NON-FINAL.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The New Matter rejection of claims 80-82, made in section 5 of the previous office action is moot in view of the amendments to the claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

New Matter

5. Claims 85 and 86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER Rejection.

Newly added claims 85 and 86 which are drawn to detecting either one of the sequences of SEQ ID NOS 1-5 in a test sample or a sequence that hybridizes to such in a test sample, further recite "determining whether a [the] polynucleotide is present in an inappropriate body compartment". This recitation is not supported by the specification at the time of filing and introduces new matter into the claimed invention because the specification does not provide support for a method of detecting a polynucleotide in an inappropriate body compartment or to determining if a polynucleotide, present in a test sample, is present in an "inappropriate body compartment" or to using the method to detect breast disease.

The claims are drawn to detecting a polynucleotide in an inappropriate body compartment and also to determining if the presence of the polynucleotide in a test sample indicates the presence of that polynucleotide in an inappropriate body compartment. A thorough review of the specification reveals that the specification contemplated methods of detecting BS106 nucleic acid in a sample, (see page 28, line 20); generally detecting BS106 (see pages 22-23), detecting breast cancer by detecting BS106 using antibodies (page 11, line 16), and

detection of the marker in tissues, cells, body fluids and secretions (page 11, line 4) blood, plasma, or serum (page 88, line 1), and body fluids (page 88, line 4). It is noted that these are all general designations and do not indicate that the appearance of BS106 nucleic acid in any of these would be considered an "inappropriate body compartment". The specification does not make clear what constitutes an "inappropriate body compartment" in terms of detection of a nucleic acid or the encoded polypeptide, nor does the specification teach or suggest determining whether expression of BS106 in a test sample indicates expression in an inappropriate body compartment. In other words, the specification does not contemplate or suggest a method of determining whether expression is indicative of expression in an inappropriate body compartment or to determining what is considered an inappropriate body compartment. The specification generally contemplates that the marker may be elevated in a disease state, altered in a disease state, or be a normal protein in an inappropriate body compartment (page 88, lines 6-7), but never sets forth the detection of the *nucleic acid* in an inappropriate body compartment, or what is considered an inappropriate body compartment. The specification teaches that Northern Blot analysis using SEQ ID NO 1 (Figures 3A and 3B) showed detection in normal breast tissue, a prostate cancer sample, and 2 out of 6 cancerous breast samples. However, the specification provides no indication that detection in any of these tissues is considered "an inappropriate body compartment", or what other tissues might generally or specifically be considered an inappropriate body compartment, or how to determine what they are. Further, with regard to claim 86, no indication is given in the specification that the detection using SEQ ID NO 1 in the cancerous prostate sample is an indication of breast disease. Further, the recitation of "a normal protein in an inappropriate body compartment" encompasses secreted protein in an inappropriate

body compartment, but provides no indication that a polynucleotide sequence encoding the protein would be contemplated or expected to be present in an inappropriate body compartment. Consequently, this amendment has introduced new matter into the claims.

Response to Arguments

6. With regard to applicant's assertion at paragraph 3 of page 6 of the response filed August 30, 2004, it is noted that the recitation at page 87, line 33, to page 88, line 7 neither contemplates a method for determining what an inappropriate body compartment is, nor that the marker is a polynucleotide in an inappropriate body compartment.

Enablement

7. Claims 80-82 and newly added claims 85-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands,* 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

The claims are broadly drawn to a method of detecting the presence of a any "BS106" gene product in a test sample (claim 80), a method of detecting generally any breast disease by determining if a any "BS106" gene product is present in a sample (claims 82 and 82), a method of determining whether a polynucleotide is present in an inappropriate body compartment (claim 85) or using this method to detect generally any breast disease (claim 86).

With regard to the term "BS106" (claims 80-82), this term is broadly defined in the specification, for example, the specification teaches at page 10, lines 30-31 that a "BS106 gene" or a fragment thereof is DNA which can have minimally 50% identity to SEQ ID NO: 4. Therefore, the claims also broadly encompass detection of a sequence that has minimally 50% identity to SEQ ID NO: 4 being indicative of the presence of a breast cell in a tissue other than breast tissue, as well as a breast malignancy. 50% identity requires only half of the same nucleotides of a specific sequences and encompasses splice variants, SNPs, mutations, deletions, insertions which may have different diagnostic implications on the nucleic acids. However, the specification provides no analysis of variants of any of SEQ ID NOS 1-5. The term "BS106" is not an art recognized term and thus the prior art is silent with respect to structural and functional features that may be used to identify such polynucleotides. Likewise, the specification provides no guidance of how to determine that a polynucleotide or a protein is a BS106 gene product, other than by % identity, nor how to use a method that determines, for example, that a polynucleotide that has only 50% identity with any of SEQ ID NO: 1-5, for example, is present in a test sample. The specification does not teach that a nucleic acid that has minimally 50% identity to any of SEQ ID NOS 1-5 is either specific for breast cells, or is an indicator of any

breast disease, or breast cancer. Additionally, the art does not support a universal correlation between expression levels of genes and their splice variants in cancer.

The claims additionally are broadly drawn to a method of detecting any breast disease wherein the presence of a "BS106 gene product" in *any* test sample is indicative of any breast disease (claim 81) or to using *any* test sample in determining whether the detection of any of SEQ ID NOS 1-5 or a nucleic that hybridizes to such is present in an inappropriate body compartment, and that such is indicative of breast disease (claim 86). The term breast disease broadly encompasses any disorder of the breast and further includes not malignant growths such as cysts, as well as breast cancer. The specification has provided no working examples demonstrating, or any predictable correlation that the detection of "BS106" in general, or SEQ ID NOS 1-5, is indicative of any of these breast diseases. The specification teaches that SEQ ID NOS 1-3 are overlapping clones that result in a consensus sequence of SEQ ID NO: 4 (see page 55). The specification teaches that SEQ ID NO: 4 was compared to an EST database and was found in 85.7% of breast libraries and only .2% of non breast libraries. The specification teaches that total RNA was obtained from solid breast tissue and from non-breast tissue and used for Northern Blot analysis and RT-PCR. Figures 3A and 3B show results of a Northern Blot analysis using SEQ ID NO: 1 as a probe with RNA from normal breast tissue, normal prostate and cancerous prostate (3A) and from normal breast and cancerous breast tissue (3B). However, the figures show that the probe hybridized to all normal breast, a prostate cancer sample, and only 2 out of 6 breast cancer samples. Therefore, from such data it is clear that the mere presence of a "BS106" gene product or any of SEQ ID NOS 1-5 is not indicative of any general breast disease or breast cancer in *any* test sample as SEQ ID NO: 1 showed hybridization in

normal breast and cancerous prostate samples. Furthermore, nowhere does the specification contemplate or disclose that the expression of SEQ ID NO: 1 in the cancerous prostate was indicative of any breast disease or breast cancer. While Table 1 indicates that overexpression corresponding to hybridization with SEQ ID NO: 1 occurred in two malignant breast samples, table 1 also shows that expression on the order of expression in normal breast was found in one malignant breast sample, and that in a second malignant breast sample, no expression was found. Therefore, the specification further fails to establish that overexpression of SEQ ID NO: 1 is diagnostic or breast disease or breast cancer in general, but is dependent upon the sample used.

The claims are further drawn to determining whether a polynucleotide is present in an inappropriate body compartment (claim 85) as well as using such to diagnose breast disease (claim 86). However, The specification does not teach or provide any working examples of a method of determining whether expression is indicative of expression in an inappropriate body compartment or to determining what is considered an inappropriate body compartment. The specification generally contemplates that the marker may be elevated in a disease state, altered in a disease state, or be a normal protein in an inappropriate body compartment (page 88, lines 6-7), but never sets forth the detection of the *nucleic acid* in an inappropriate body compartment, or what is considered an inappropriate body compartment. The specification teaches that Northern Blot analysis using SEQ ID NO 1 (Figures 3A and 3B) showed detection in normal breast tissue, a prostate cancer sample, and 2 out of 6 cancerous breast samples. However, the specification provides no indication that detection in any of these tissues is considered "an inappropriate body compartment", or what other tissues might generally or specifically be considered an inappropriate body compartment, or how to determine what they are. Further, with regard to

claim 86, no indication is given in the specification that the detection using SEQ ID NO 1 in the cancerous prostate sample is an indication of breast disease. Further, the recitation of "a normal protein in an inappropriate body compartment" encompasses secreted protein in an inappropriate body compartment, but provides no indication that a polynucleotide sequence encoding the protein would be contemplated or predictably expected to be present in an inappropriate body compartment.

As the art is silent with regard to expression of a "BS106" gene product or SEQ ID NOS 1-5, the art does make up for the deficiencies in the specification.

Therefore, given the lack of guidance in the specification or the art as to a method of detecting any breast disease or breast cancer by detecting a 'BS106 gene product" or a method of determining if the presence of any of SEQ ID NOS 1-5 or a sequence that hybridizes to such is in an inappropriate body compartment, the use of such to diagnose any general breast disease, or breast cancer, or how to determine what constitutes an inappropriate body compartment, the skilled artisan would be required to perform undue experimentation to practice the invention as claimed. Firstly, the specification provides no evidence that a nucleic acid with minimally 50% sequence identity to any of SEQ ID NOS 1-5 is specifically expressed only in breast disease, or how to use a sequence with minimally 50% identity to any of SEQ ID NOS 1-5. Furthermore, the specification has not established that either the mere presence of BS106 in any tissue sample, including breast, or the overexpression of BS106 in any sample, including breast, is predictably associated with breast cancer, let alone any general breast disease. Additionally, the specification has not established what constitutes an inappropriate body compartment or that that the presence of any of SEQ ID NOS 1-5 in an inappropriate body compartment is predictably

correlative of breast disease (for example, the specification teaches expression in cancerous prostate, but is silent as to any indication of breast disease or breast cancer). Therefore, a large amount of trial and error analysis, the results of which are unpredictable, would be required of the skilled artisan to determine if any sequence which minimally only has 50% identity to any of SEQ ID NOS: 1-5 would be diagnostic of any breast disease, or specifically breast cancer in any test sample. Given the minimal disclosure in the specification, and the lack of any teaching in the art, it would further be unpredictable if the presence of BS106 in *any* test sample was indicative of a breast malignancy, or determining which test samples constituted an "inappropriate body compartment". As such, the experimentation required by the skilled artisan to make and use the invention is considered undue.

Response to Arguments

8. In the response dated 5/6/2002, a declaration by Dr. Paula Friedman, under 37 CFR 1.132 was submitted. The Declaration provided data showing that the results of experiments conducted on lymph node tissue from breast cancer patients and non breast cancer patients to detect the presence of BS106 RNA. The results show that detection of BS106 is correlated to detection of metastatic breast cells in lymph nodes. However, the declaration fails to provide evidence that the claims were enabled *at the time of filing of the instant application* because the specification has only asserted the use of BS106 for detecting breast tissue and breast cancer by detecting BS106 in breast tissue. The specification does not describe or contemplate testing lymph nodes nor that such would constitute an "inappropriate body compartment". The specification does not provide any teaching that BS106 was specifically contemplated to be associated with metastatic breast tumors, but instead asserts its association to breast cancer in breast tumors from

breast tissue. As stated in In re Glass, 181 USPQ 31, (CCPA 1974), "if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date." Further, the declaration provides no predictable correlation that diagnosis of breast cancer would also be predictive of any general breast disease.

The response filed August 30, 2004 asserts that the expression of a marker in a tissue or body compartment where their normal occurrence is very low or non-existent indicates that a disease has altered the marker. This argument has been thoroughly reviewed but was not found persuasive. Firstly, applicants have provided no evidence to support that such an occurrence is predictably correlative of disease or what or how to determine what that disease might be. Secondly, it is noted that the arguments of counsel cannot take the place of evidence in the record. See *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). By way of examples, the response sets forth that PSA is normally expressed in seminal fluid and in blood at very low levels, but that in patients with diseases the expression in blood is elevated. The response further asserts that CEA is a normal component of the inner lining of the colon and is present in stool and blood in low levels, but that in patients with disease of the colon, the concentration is markedly elevated in the blood plasma or serum. The response further asserts that these markers are still recognized as useful in the diagnosis of their primary tissue of origin. These arguments have been thoroughly reviewed but were not found persuasive. Firstly, it is noted that the diagnostic utility of PSA and CEA represents extensive analysis with regard to two

very highly characterized markers. As discussed above, the specification as originally filed only provided evidence that SEQ ID NO 1 could be used to determine expression in normal breast, cancerous prostate, and elevated expression in certain breast cancer samples. No teaching or suggestion of the ability to use SEQ ID NO: 1 to establish breast cancer metastasis to lymph node was provided by the specification at the time of filing. While there is no per se requirement as to how much analysis is required to determine diagnostic utility, case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". In the instant case, the specification has provided no teaching that expression or that elevated expression of SEQ ID NOS 1-5 or "BS106" is predictably diagnostic of any breast disease, let alone breast cancer, by detecting expression in any test sample. Further, the specification has provided no teaching that the nucleic acids of SEQ ID NOS 1-5 of BS106 are found in any "inappropriate body compartment" or what such an inappropriate body compartment might be, or that detection in such is predictably diagnostic of any breast disease, breast cancer, or breast cancer metastasis to lymph node. The response appears to try to draw sweeping conclusions based on the utility of PSA and CEA that a marker that is expressed in both cancerous and non cancerous tissue is useful in the diagnosis of disease of their primary tissue of origin due to their strong tissue selectivity. However, the specification has enabled the skilled artisan to make or use the

invention as broadly as it is claimed for the reasons made of record above and in previous office actions.

Conclusion

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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10/28/04